Accelerating Regulatory Pathway for Biologics and Biosimilar Drugs

AIDCOC
Training Academy

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Accelerating development in Biologics Regulatory

Regulated Industry work is

governed by Rules and regulations

Pharma & Biologics Industry

must comply to

Acts, Rules, Schedules, Guidelines, etc.,

CDSCO Mission

Regulatory Bodies involved in Biologics

Under Ministry of Health and Family Welfare

DCG(I) Drug Controller General of India, CDSCO

- Monitors product safety and efficacy
- Approval for Clinical, Mkt. authorization of drugs
- Post Approval change approvals

NIB Noida (National Institute of Biologics)

- Biological product testing

CDTL Kasauli (Central Drug Testing Laboratory Kasauli)

- Testing of Vaccines and Sera products

IPC Gaziabad (Indian Pharmacopoeia Commission)

- Establishment of monograph for Biosimilar and Biologicals

Other Ministries involved

GEAC (Genetic Engineering Advisory Committee)

- Under Ministry of Environment & Forest
- Approval of products with Live Modified Organisms

RCGM (Review Committee for Genetic Manipulation)

- Under Ministry of Science and Technology
- Monitoring of cloning development
- Approval of Preclinical studies (if r DNA)

State FDCA (Food & Drugs Control Administration)

- Under State MOHFW
- Grants Manufacturing License, WHO GMP certificate, COPP
- Audit of plants

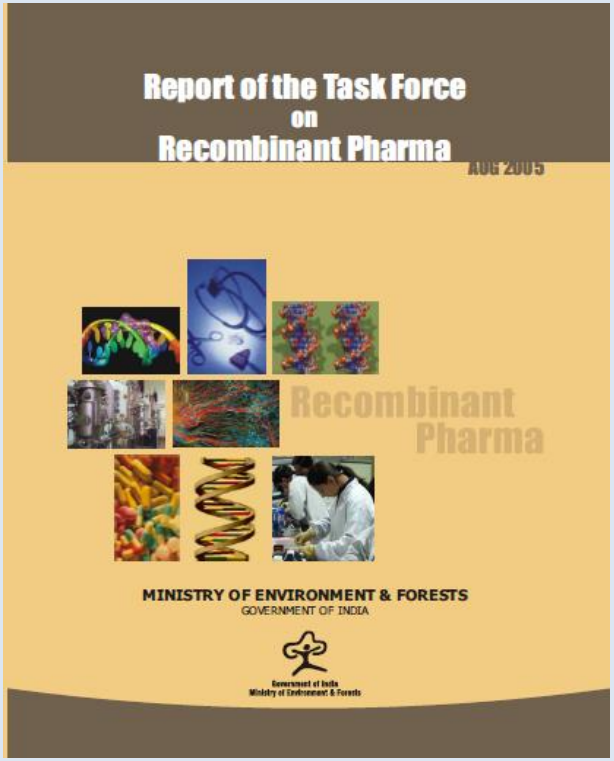
Biologics Applicable Guidelines

Rules and Regulations

- Drugs and Cosmetic Act, MOH&FW 1940 and amendments
- Drugs and Cosmetics Rules, MOH&FW, 1945
- Recombinant DNA Safety Guidelines, DBT, 1990.
- Guidelines for generating preclinical and clinical data for rDNA vaccines, diagnostics and other Biologicals, MOEF, 1999
- Revised Schedule M introduced for Good Manufacturing Practices, CDSCO amended in 2001 and implemented 2005

New Guidelines - Biologics

Steps and actions taken for Quality, Safety and Efficacy



Report of the Task Force on Recombinant Pharma. 2005 Chaired by Dr. R. A. Mashelkar

The step-wise regulatory procedures protocols for five scenarios & Agencies involved

1. Indigenous development – Product is not LMO
2. Indigenous development – Product is LMO
3. Import and Marketing of Finished product – Product is LMO
4. Import and Marketing of Bulk product – Product is LMO
5. Import and Marketing of Finished product – Product is not LMO

Documents to be submitted by the applicant to the regulatory authorities for obtaining clearances

New Guidelines - Biologics

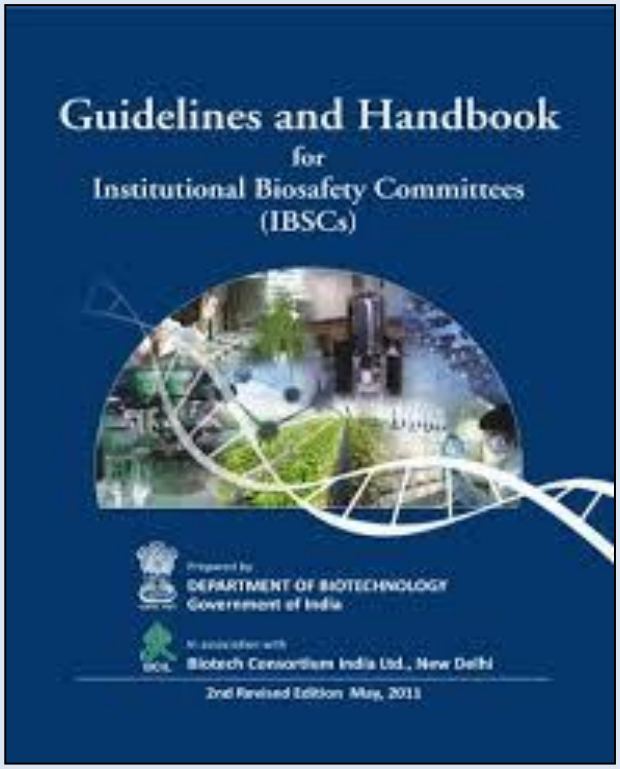
Steps and actions taken for Quality, Safety and Efficacy

CDSCO guidance for industry: Biotechnological /Biological Products, 2008

- Submission of Clinical Trial Application (CTD format)
- Submission of New Drug Approval (CTD format)
- Post approval changes in Biological products: Quality, Safety and Efficacy Documents
- Preparation of Quality Information for submission

New Guidelines - Biologics

Steps and actions taken for Quality, Safety and Efficacy



Guidelines and Handbook for Institutional Biosafety Committees (IBSCs), 2011

- Establish Biosafety requirements
- Clear guidance on Institutional Biosafety Committees (IBSCs)
- New forms for individual activities

New Guidelines

Steps and actions taken for Quality, Safety and Efficacy

- Pre-screening of application was initiated in Nov. 2011
- DCG(I) created New Drug Advisory Committees (NDACs)) for review and evaluation of Clinical Trial applications effective Dec. 2011

New Guidelines

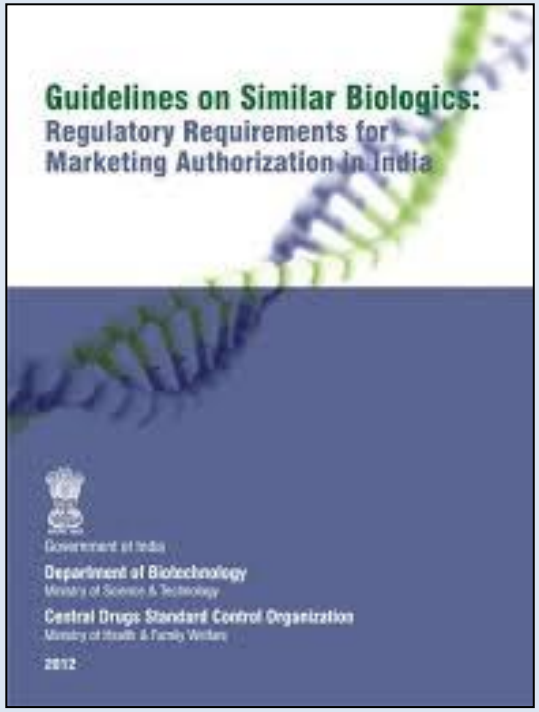
Steps and actions taken for Quality, Safety and Efficacy

Supreme Court Order

- **Supreme Court order (2013):**
  - Stayed ~ 157 CTs in India
- Supreme court / Parliamentary committee proposed several changes
- **A three-tier process for reviewing and evaluating CT applications (2014):**
  - **Subject Expert Committees (SECs) / IND for novel products**
    Role: Review of CT and Marketing Authorization application
  - **Technical Committee (TC)**
    Role: Review & endorsement of decision by SEC, Hear Appeal of firm
  - **Apex Committee**
    Role: Review & endorsement of decision by SEC and TC

New Guidelines - Biologics

Steps and actions taken for Quality, Safety and Efficacy



Guidelines on Similar Biologics: Regulatory Requirements for marketing authorization in India

2012

Guidelines on Similar Biologics: Regulatory Requirements for marketing authorization in India

2016

Difference between 2012 & 2016

- Abbreviated analytical comparability not accepted
- Phase III requirement (100 test arm - comparative)
- Mandatory Phase IV (200 patients - single arm)
- Critical Quality Attributes (CQA) and Key Quality Attributes (KQA) requirement specified

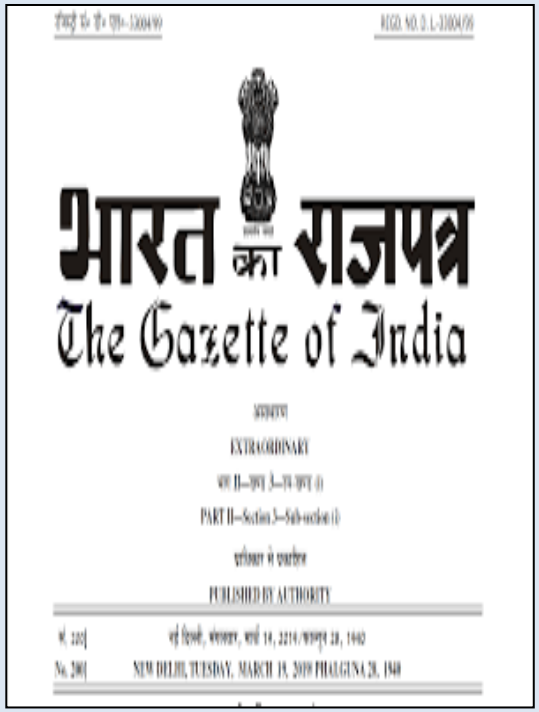
New Guidelines

Steps and actions taken for Quality, Safety and Efficacy

Sugam portal: Online portal for submission introduced 2017

New Guidelines

Steps and actions taken for Quality, Safety and Efficacy


भारत का राजपत्र
The Gazette of India
EXTRAORDINARY
PART II—Section 3—Sub-section (i)
PUBLISHED BY AUTHORITY
NEW DELHI, TUESDAY, MARCH 19, 2019/PHALGUNA 28, 1940

New Drugs and CT Rules, 2019

Key items introduced

- Pre-approval and post trial access
- Pre-submission and Post-submission meeting introduced
- Time bound approvals for CT
- More reporting of clinical trials
- Clarity of Phase IV and Post marketing studies

Recent notification for fast track approval of Form 29

Regulatory Reforms required

- Removal of unnecessary permissions and licenses (Form 29)

- Risk based relaxation (Stock pilling)

- Time bound approvals (CT and MA)

- Adopt ICH guidelines & become member of ICH & PICS

- Leader in Regulatory policy & innovation (interchangeability)

- Policies for promotion of NCE and NBE development

New Policies required

for accelerating Biologics and Biosimilar Development in India

- NOC for Form 29 and Form 29 for R&D – self declaration
  Not required anywhere in the World
- Animal study approval for r DNA products – not required for Pharma
  Not required anywhere in the World
- Stock pilling before MA and ML (Biologics mfg. and testing takes months)
  Similar to US-FDA
- E- Package insert instead of Hard copy
  Singapore has published guideline for e-labelling
- Singe Window process (Several Agencies involved right now)
- Introduction to Interchangeable to Similar Biologics Guideline, India

Biologicals Success stories - India

Biologicals: Success story of India

World Leader in Vaccines – Self sufficient and one of the key distributors to UNICEF – Products all over world. Serum Institute, Bharat Biotech, etc.

Significant player in Biosimilars – Biosimilars launched in India and Emerging markets, Few companies also entered US and EU market

New Entrant in novel biologics – Biocon, Bharat Serums and Vaccines, Cadila Healthcare Ltd.

New Entrant in Newer therapies - Cell-based & Genetherapy

Like Pharma, Biologicals also set to make India proud

Biologicals Impact in 2021

Industry

- Collaborations and Tie up
- Good research
- Multiple approaches
- Parallel development
- Quick resolution
- Initial engagement with Regulators
- New own Facility & Outsourcing
- Production – Stock pilling
- Rapid enrolment of patient
- Alternate vendor development

Regulators / Government

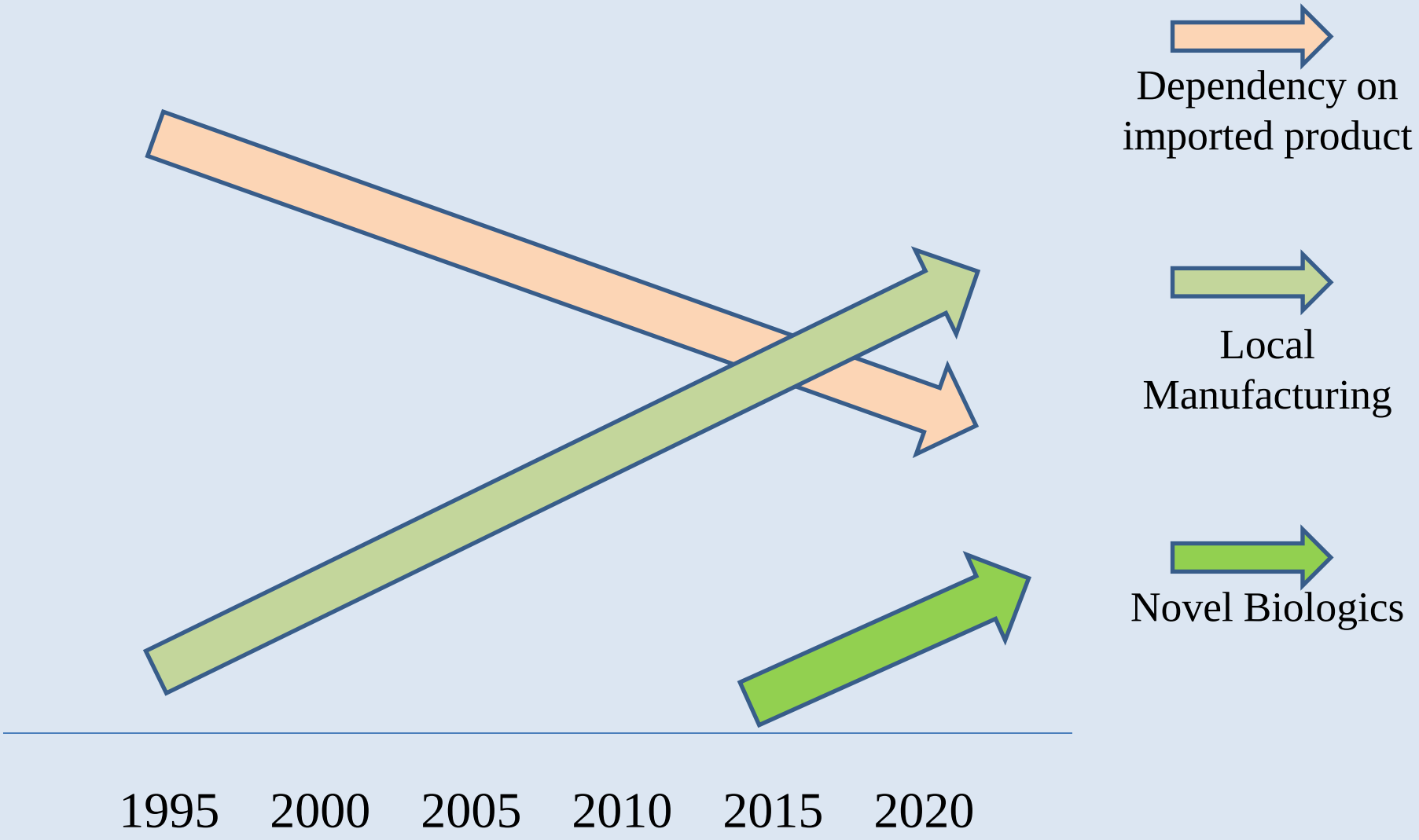
- Covid task force
- Setting Guidelines
- Quick review
- Risk based relaxation
- Stock pilling permission
- SEC meetings in a week
- Emergency Use Authorization based on Interim Phase III
- Work with Industry
- Relaxation in export permissions

Able to develop vaccine NBE in record time

India has emerged as Vaccine Mfg. Hub of the World

Delivered Safe and Efficacious Covid vaccine for world

Indian Biologics Scenario



Biosimilar battles

Won a few, still few fights ongoing

Battles	India	EU / US
Scientific	Won	Won
Parliament	Won	Won
Regulatory	Won	Won
Legal / Patent	Won	Won
Physician	Won	Partial
Pharmacist	Won	Partial
Patient	Won	Partial

Indian companies who have received Biosimilar approvals in EU / US / Japan so far

INTAS

Biocon

LUPIN

USV

Other market battles:

- Innovator companies
- Biosimilar companies
- Second generation & improved versions
- New Chemical molecules targeted for same indication

Biologicals development regulatory requirement

What is Biologicals?

“Use of cellular and molecular processes in biological systems to make products”

Biologicals Product Classes

- **Current products are mostly**
  - **Non- recombinant**
  - **Recombinant**
  - **New Product Class**

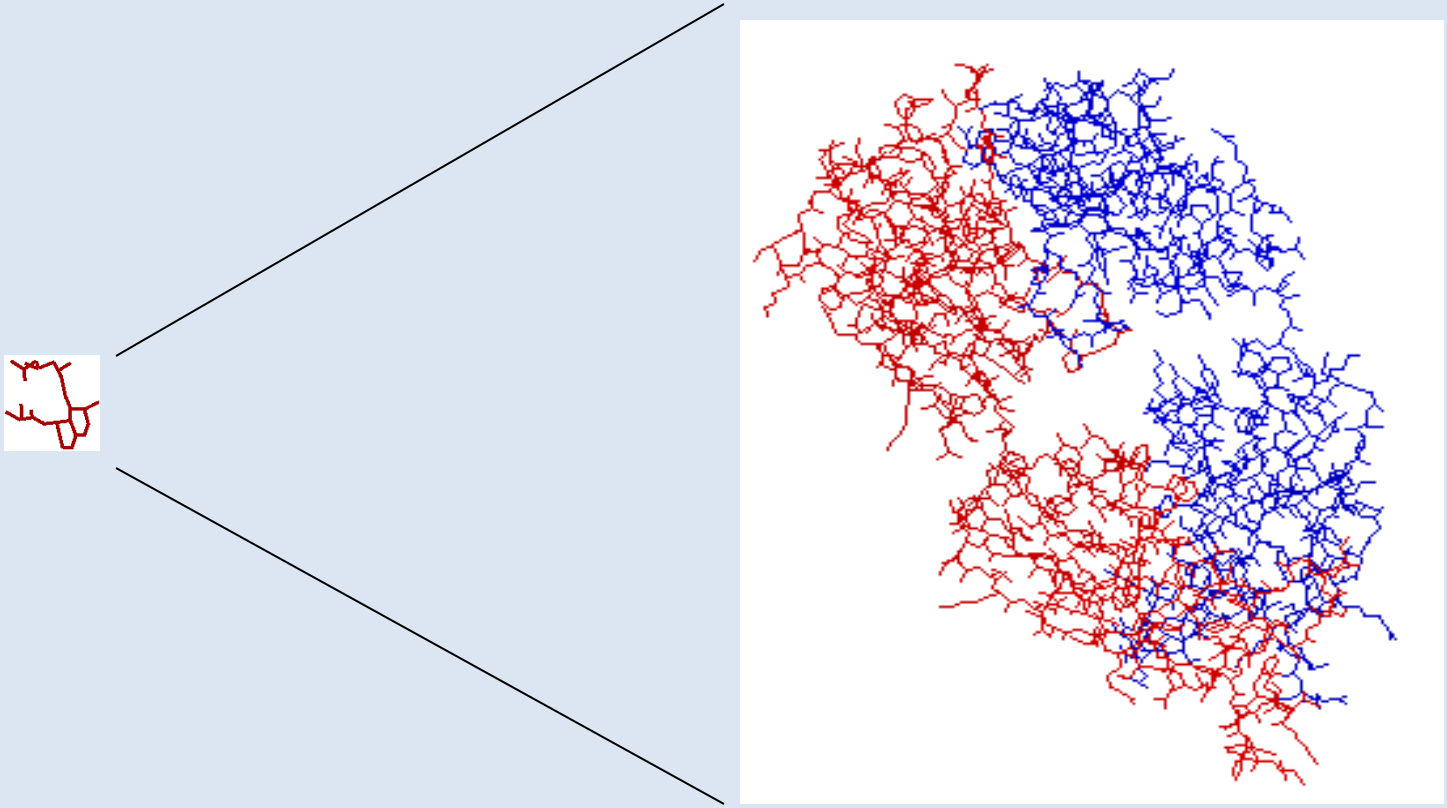
API
comes from
Biological source

- **Non-Recombinant Biologicals**
  - **Cytokines & hormones – Urine derived**
  - **Human or Animal derived - Blood proteins, Antibodies and factors**
  - **Vaccines – Live Attenuated, Inactivated or killed, cellular fractions**
- **Recombinant Biologicals: Cytokines, hormones, mAbs, vaccines**
  - **Recombinant bacterial, yeast, mammalian, transgenic animal**
- **New product classes: Cell based therapies & Genetherapy**

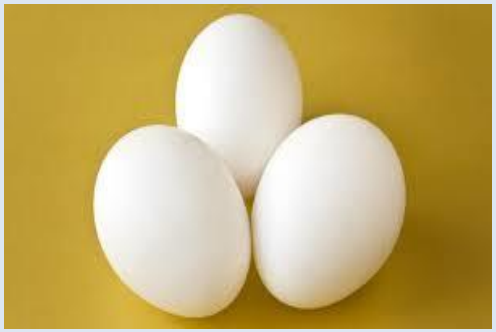
Biologicals are big molecule

Pharma molecule

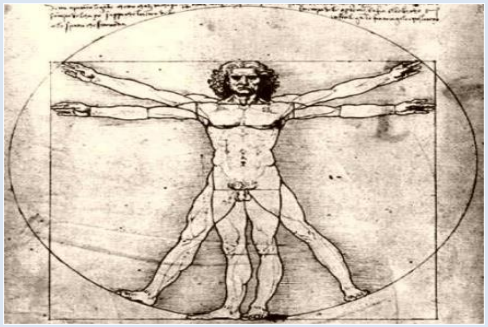
Biological molecule



Starting material is of biological origin

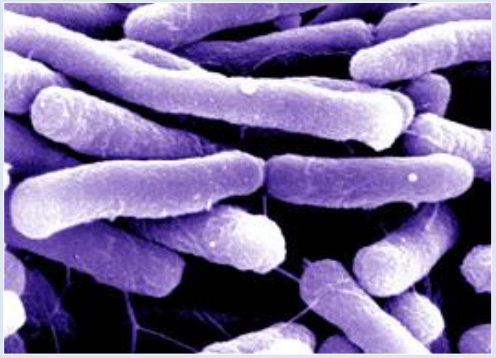


Egg

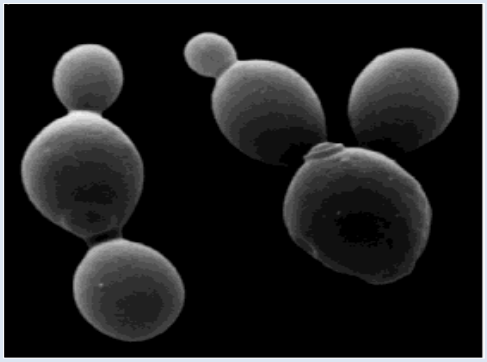


Humans

Mammalian cell-culture



Bacteria



Yeast

Transgenics

Why are Biologicals of interest?

- >$200 billion total market (Several “blockbusters” >$5 billion)
- Largest drug Adalimumab, 2020 yearly revenue $19.8 billion
- Specialized applications, often not replaceable by chemical drugs
- Generally low volume, high value products
- >100 products approved, >500 in development
- ~40% drugs are cancer related
- >50% of new drugs in coming 20 years will be Biological drugs
- Biologics are difficult to produce and hence usually get higher margins

Biologicals is a vast field,

Today, I will cover Biosimilars

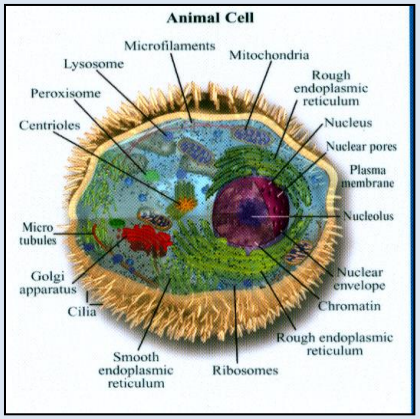
Biosimilar starting material

Live Cell

Cloning has 3 key components:

- Cell line: *E. coli* / CHO
- Vector: Plasmid
- Gene of interest: G-CSF / EPO / mAb

Cloning results in Master culture



From master culture, cell banks are produced

- Research Cell Bank
- Development Cell Bank
- Master Cell Bank
- Manufacturer's Working Cell Bank

Biosimilar Manufacturing Processes

- Drug Substance process
  - Upstream Process (cell culture / fermentation)
  - Downstream Process (protein purification)

The process output is Drug substance or Bulk or API which is starting material for Drug Product

Upstream – Bioreactor Process

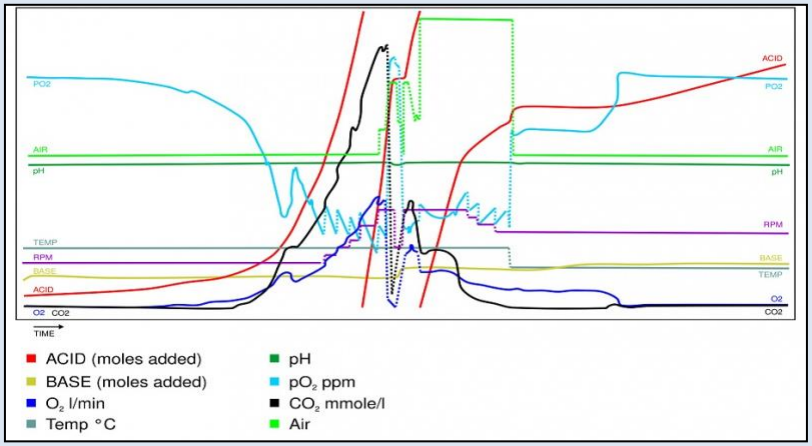
Process Iteration

Process Optimisation

Pilot Process

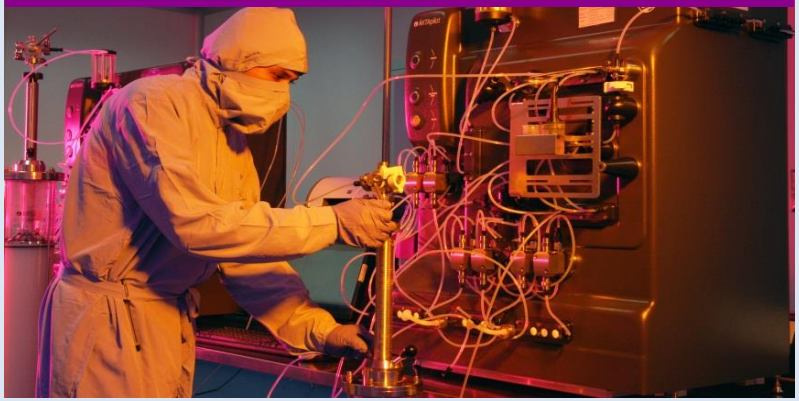
Scale-up

Process Controls



Downstream - Protein Purification

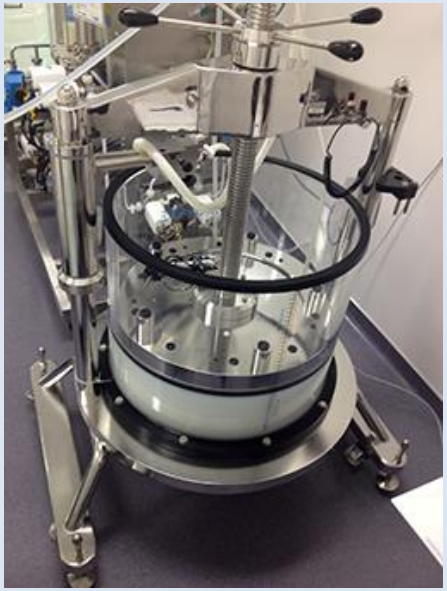
Purification Systems



Tangential Filtration

Centrifugation

Columns



Biosimilar Manufacturing Processes

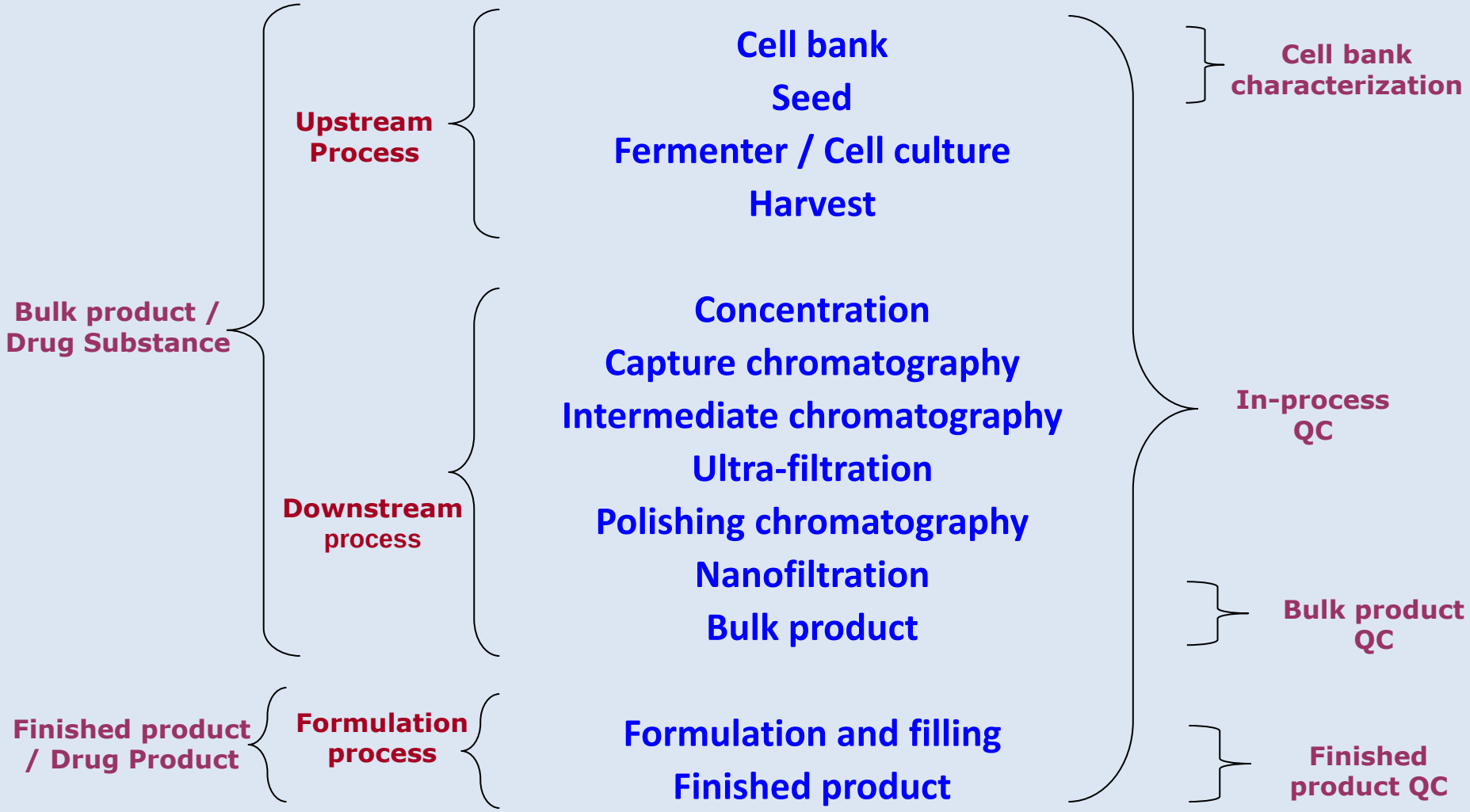
- Drug Product process
  - Liquid
    - Vial

    - Prefilled syringe

    - Cartridge with Pen device

  - Lyophilized
    - Vial

Typical Biosimilar Product Mfg. Process



Specifications of Drug Substance

Characters
- ☐ Physical Appearance
- ☐ pH

Assays
- ☐ Protein Concentration by UV absorption
- ☐ Specific Activity (By In-vitro bioassay)

Identity
- ☐ SDS-PAGE (Non Reducing)
- ☐ Isoelectric Focusing
- ☐ RP-HPLC
- ☐ Peptide Mapping
- ☐ Immunoblotting
- ☐ SDS-PAGE (Non Reducing)

Purity
- ☐ SDS-PAGE (Non Reducing)
- ☐ SDS-PAGE (Reducing)
- ☐ RP-HPLC
- ☐ SEC-HPLC
- ☐ Host Cell Protein
- ☐ Residual DNA

Safety
- ☐ Bacterial Endotoxin
- ☐ Bioburden

Other test
- ☐ Glycan Analysis
- ☐ Charge variant

Specification has 2 components: a) Method b) Acceptance Criteria

Specifications of Drug Product

Characters

- ☐ Physical Appearance
- ☐ pH
- ☐ Volume

Assays

- ☐ Protein Concentration by UV absorption
- ☐ Specific Activity (By In-vitro bioassay)

Identity

- ☐ Immunoblotting (By Slot Blot)
- ☐ RP-HPLC

Purity

- ☐ Related Impurities (By RP-HPLC)
- ☐ SEC-HPLC

Safety

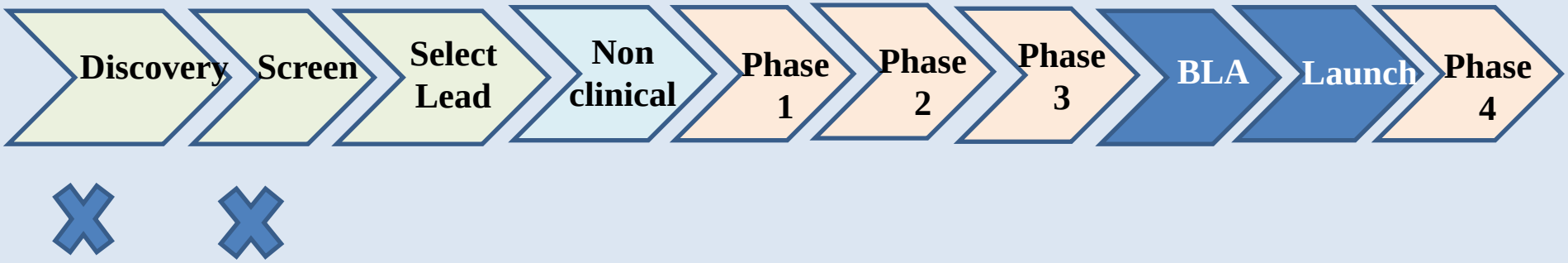
Microbial Test

- ☐ Bacterial Endotoxin
- ☐ Sterility
- ☐ Particulate Matter

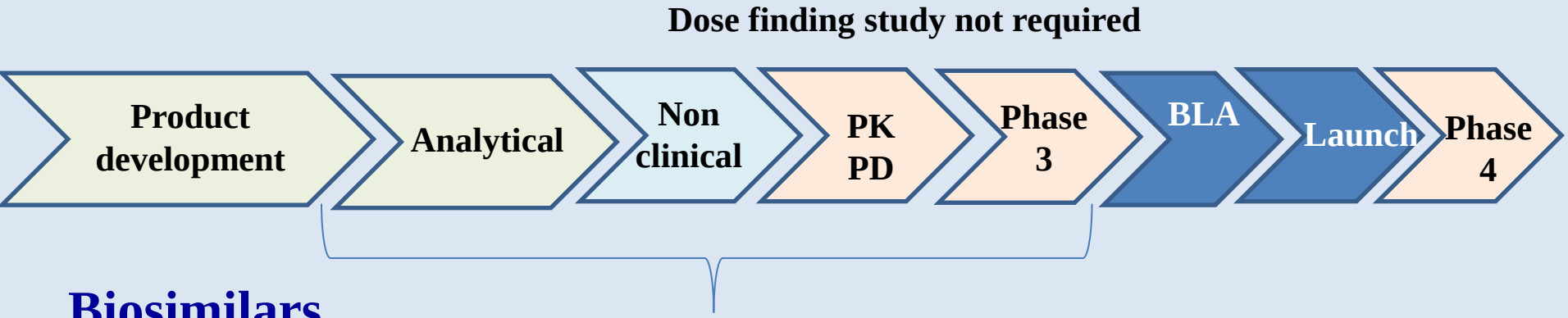
Specification has 2 components: a) Method b) Acceptance Criteria

Difference in development

Novel Biologics

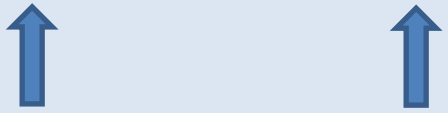


Biosimilars



GxP

Discovery	Research & Development	Animal Studies (Pharm. & Tox.)	Clinical Studies (Phase 1, 2 & 3)	Manufacturing & Market
GDP	GDP	GDP	GDP	GDP
		GLP		
			GCP	
			GMP	GMP



IND / CTA BLA / MAA

Stages of Biosimilar Development - 1

Clone Development

Analytical Development

Process Development Drug substance

Process Development Drug Product

Process, Methods and Specification finalization

Begin with the end in mind

Quality by Design Approach

IBSC permissions

RCGM notifications

Test License

Stages of Biosimilar Development -2

Consistency Batches

Analytical Similarity

RCGM meeting

Non-Clinical Similarity

RCGM meeting

Clinical Trial Similarity

(PKPD & phase III)

SEC meeting

MAA submission

SEC meeting

Audit of facility

Mkt. Authorization, Mfg. License & Launch

CMC and GMP requirements

Validation of methods and process

Pre-approval Inspections

Biosimilar development

as per Similar Biologics Guideline, India

Once the biosimilar product is developed, the firm needs to prove Similarity of Biosimilar product to Reference Medicinal product

- **Analytical Similarity**
- **Non-clinical Similarity**
- **Clinical Similarity**

for Approval of Biosimilar product

Analytical Similarity

as per Similar Biologics Guideline, India

Consists of

- Physico-chemical characterization
- Biological Characterization

- Orthogonal analytical tests

Several batches > 6 head to head comparison

- Biosimilar
- Reference Medicinal product

Statistical comparison needs to be shown

Non-Clinical Similarity

as per Similar Biologics Guideline, India

- ❑ Single dose toxicity (dose tolerance)
- ❑ Repeat dose toxicity (also with recovery period)
- ❑ Local Tolerance
- ❑ Allergenicity

Safety pharmacology, reproduction toxicology, and carcinogenicity studies are not required for Biosimilars

Regulatory considerations

- Two relevant species
- Route of administration resembling clinics (IV / IM / SC)
- Control animals in each study (vehicle control)

Comparative studies are mandatory,

Relevance of toxicity studies is reducing for Biosimilars if the product is highly similar

Clinical Similarity

as per Similar Biologics Guideline, India

- **PK PD study** is required in Healthy volunteer
- **Phase 3 clinical trial** is required (Safety and Efficacy with Immunogenicity)
  - 100 patients in test arm is sufficient
  - Comparative study is mandatory
- **Phase 4 study** in 200 patients (Safety)
- Subject Expert Committee reviews
  - Clinical trial protocol
  - Clinical trial report – for recommending for Marketing authorization

Dose finding study
is not required for Biosimilars

Extrapolation to other indications

as per Similar Biologics Guideline, India

If >1 indication is approved for Innovator,
Extrapolation to other indication is allowed in India & World

Extrapolation is based on complying on following conditions:

- Biosimilarity established in Analytical similarity
- Biosimilarity established in animal toxicity studies
- Biosimilarity established in at least one clinical indication
- Mechanism of action is same
- Involved receptors are same

Biologicals Application & Approvals

(Indigenous developed products - India)

Stage	Agency	Applications	Approvals
Carrying out R&D	RCGM	Form C1	Form C2
NOC for Test License (R&D)	CDSCO	Form CT-10	Form CT-11
Test License (R&D)	State FDA	Form 30	Form 29
Preclinical Permission	RCGM	Form C3	Form C4
Submission of Preclinical report	RCGM	Form C5	Form C6
NOC for Test License for CT	CDSCO	Form CT-10	Form CT-11
Test License for CT	State FDA	Form 30	Form 29
Clinical Trials (Phase 1 / 2 / 3)	CDSCO	Form CT- 04	Form CT- 06
Import License for CT	CDSCO	Form CT-16	Form CT-17
Marketing Authorization (MA)	CDSCO	Form CT-21	Form CT- 22 / 23
Manufacturing License (ML)	State FDA	Form 27D	Form 28D

R&D	Animal Studies	Clinical Trials	MA and ML

Biologicals Application & Approvals

(Imported products to India)

Stage	Agency	Applications	Approvals
Clinical Trials (Phase 1 / 2 / 3)	CDSCO	Form CT-04	Form CT-06
Import License for CT	CDSCO	Form CT-16	Form CT-17
Marketing Authorization (MA) *	CDSCO	Form CT-18	Form CT-19 / 20
Registration Certificate (RC) *	CDSCO	Form 40	Form 41
Import License (IL) *	CDSCO	Form 8 and 9	Form 10

* Can be submitted in parallel

Clinical Trials	MA, RC, IL

Thank you